REMARKS

Claims 1-11 were present in the application as originally filed and were pending in the application. Claim 5 is canceled above; as a result, claims 1-4 and 6-11 remain pending in the application.

The Office Action contains the statement that features upon which Applicants' earlier arguments rely, for example, "normalization step to provide for pretreatment fibrinogen levels" and "treatment on a human patient", are not recited in the claims. In response, Applicants note that independent claims 1 and 9 contain the language "allowing normalization of fibrinogen levels to occur without further administration of said defibrinogenating agent." Inherent in the term "normalization" is the concept of the return to normal, (i.e., pre-treatment) basal levels.

Claims 1 and 9 are amended above to clarify that treatment is for a human subject or patient.

Rejection Under 35 U.S.C. §103(a)

Claims 1-11 were rejected under U.S.C. §103(a) as allegedly being unpatentable over Elger in view of Schwartz et al (U.S. Patent No. 5,523,292).

According to the Office Action, it would have been obvious to one of skill in the art at the time the claimed invention was made to treat stroke with ancrod as allegedly disclosed by Elger by selecting for the time intervals and effective amounts which were shown to be effective in reducing restenosis as taught by Schwartz. Applicants disagree.

The novelty of the present invention lies in the administration of ancrod to achieve a specific defibrinogenation pattern associated with improved safety and efficacy. Claim 1 is amended above to focus the method on a specific rate of administration of defibrinogenating agent that will result in the desired rate of defibrinogenation. Support for the amendment is found in former claim 5, which is now cancelled.

Elger et al. reports the results of an evaluation of whether or not treatment with the fibrinogen-lowering agent ancrod exerts beneficial effects on experimentally induced brain lesions in two different rat models of focal cerebral ischemia. Lesions were induced by either occlusion of the left proximal middle cerebral artery (MCA) or by photochemically induced thrombotic infarction. Subsequently, lesion volume was evaluated using MRI. There are several reasons why the teachings of Elger et al. are inapposite to the present invention.

Firstly, Applicants note that the dosages of ancrod associated with a beneficial effect in the studies by Elger are considerably greater than those required in the present method of treatment. In assessing the effect of ancrod administration following MCA occlusion, Elger teaches that intravenous infusions of ancrod (duration of 30 min) at dosages of 10, 30, 50 or 70 IU/kg produced significant reductions of total lesion volumes (page 2, col. 2.). These doses are ~10 times higher than those necessary to achieve maximal defibrinogenation in spontaneously hypertensive rats (and 10-25-fold higher than those disclosed by Schwartz et al.) as demonstrated in separate preliminary experiments to determine the time course of decrease in fibrinogen concentration in rats (bottom of page 896 bridging page 897.) For these studies, ancrod was infused at rates of 2 IU/kg/hr to 20 IU/kg/hr (Fig.1, page 897.) Elger does not teach that there is a beneficial effect, i.e., a reduction in lesion volume, at doses/rates that are within the range used in the claimed method.

Secondly, for the reasons articulated in response to an earlier Office Action, Applicants maintain that the animal model described by Elger et al. is not a representative model of acute ischemic stroke in humans. One of skill in the art would appreciate that brain hemorrhages in acute ischemic stroke in humans do not develop instantaneously. Rather, it takes a day or so for the brain to soften and for hemorrhages to develop. In employing an observation period limited to 24 hours, Elger et al. have provided an animal model that provides an incomplete picture and as such, has little or no relevance to the incidence of human intracranial hemorrhage. In a clinical stroke trial to assess the effect of ancrod, all symptomatic intracranial hemorrhages in the ancrod-treated group developed between 12 and 72 hours after beginning treatment. Elger's study, therefore, does not provide an accurate characterization of the human disease. Happily, we do not end our

observation of humans at 24 hours; if we had, we might have incorrectly concluded that the older treatment regimens did not significantly increase symptomatic intracranial hemorrhage.

To date, no successful animal study in acute, ischemic stroke has been followed by a comparably designed and successful human study. So while it might appear on its face logical to extrapolate an animal dosing regimen to humans, experience does not support that conclusion. Dosing regimens in animals are usually difficult to translate into human use and are therefore often modified considerably before being used in humans.

Schwartz et al. is cited in the Office Action for the teaching of doses of ancrod and dosage intervals that are effective in preventing thrombus formation in the coronary artery thereby reducing restenosis. According to the Office Action, the identical effective range amounts used by Applicants are disclosed by Schwartz and one of skill would have expected that the amounts would work because the same identical compound is useful to treat stroke patients. Applicants disagree.

Schwartz et al. discloses administration to pigs at a dose of about 1 to 3 units/kg of body weight with a goal of reducing the fibrinogen level to about 100mg/dL. According to Schwartz et al., the treatment group received ancrod intravenously at a rate of about 2 units/kg over 1 hour during the cutdown and subsequently 700 units were infused continuously at about 70 units/day, or approximately 3 units per hour (col. 5, lines 1-5). This administration rate is outside the range claimed by Applicants.

The major difference between the claimed dosing regimen and previous regimens used in human stroke is that in prior regimens the goal has been to achieve a given level of fibrinogen and to maintain it for several days. This is clearly the strategy in Schwartz et al.; Schwarz notes that the treatment being described aims to achieve a "desired fibrinogen level" and further emphasizes that "maintenance doses may be administered after determining the patient's fibrinogen concentration (col. lines 62-65). This terminology clearly anticipates maintaining the desired fibrinogen level over a lengthy period of time. Schwartz et al. emphasizes that ancrod must be administered relatively slowly in order to

prevent excessive coagulation (col. 2, lines 49-51). According to Schwartz, administration of ancrod may be extended 1 to 2 weeks or longer (col. 3, lines 8-12.) In contrast, the aim of the claimed method is to lower the fibrinogen rapidly without attention to an attained level and then to end the infusion without any meaintenance phases or titration against a post-treatment fibrinogen level.

Thus, a method of treating stroke using the specific ancrod administration rate claimed by Applicants to achieve a defined pattern of defibrinogenation would not have been obvious to one of skill in the art based on the combined teachings of Elger and Schwartz. Given that Elger only saw a beneficial effect using doses significantly higher that those used by Schwartz, there is no apparent reason why one of skill would conclude that the doses used by Schwartz would be effective for reducing lesions in the cerebral vasculature subsequent to an ischemic event. One of skill would not conclude based on the combined teachings of Elger and Schwartz that administration of ancrod at the rate claimed by Applicants would lead to an optimal rate of defibrinogenation and ultimately an improved outcome in stroke patients.

Withdrawal of the rejection under 35 U.S.C. §103 is respectfully requested.

Reconsideration and allowance of this application are respectfully requested in view of the remarks above. It is believed that the application is in condition for allowance, and such action is respectfully requested. If a telephone conference would be of assistance in advancing the prosecution of the subject application, the Examiner is invited to contact applicant's undersigned attorney at the number provided below.

Respectfully submitted,

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